

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



11 JAN 2005

(43) International Publication Date
22 January 2004 (22.01.2004)

PCT

(10) International Publication Number
WO 2004/006898 A3

(51) International Patent Classification⁷: **A61K 38/17**,
C07K 14/47, 16/18, G01N 33/68, C12Q 1/00

TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA,
ZM, ZW.

(21) International Application Number:
PCT/DK2003/000486

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(22) International Filing Date: 10 July 2003 (10.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2002 01092 11 July 2002 (11.07.2002) DK

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES,
FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO
patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,
ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

(71) Applicant (*for all designated States except US*): SEMA
APS [DK/DK]; Willemoesgade 33, 1th, DK-2100 Copen-
hagen (DK).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): CHRISTENSEN,
Claus [DK/DK]; Gammel Kongevej 35E, 4th, DK-1610
Copenhagen (DK). LUKANIDIN, Eugene [RU/DK];
Willemoesgade 33, 1th, DK-2100 Copenhagen (DK).
OLSEN, Ole [DK/DK]; Skovvej 77D, DK-2920 Char-
lottenlund (DK). ALBRECHTSEN, Morten [DK/DK];
Høstvej 7, DK-2920 Charlottenlund (DK).

(74) Agent: HØIBERG A/S; St. Kongensgade 59A, DK-1264
Copenhagen (DK).

Published:

— *with international search report*
— *before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments*

(81) Designated States (*national*): AE, AG, AL, AM, AT (uti-
lity model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (uti-
lity model), DE, DK (utility model), DK, DM, DZ, EC, EE
(utility model), EE, ES, FI (utility model), FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO,
RU, SC, SD, SE, SG, SK (utility model), SK, SL, SY, TJ,

(88) Date of publication of the international search report:
17 February 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

WO 2004/006898 A3

(54) Title: USE OF COMPOUNDS CAPABLE OF INHIBITING THE PROTEOLYTIC PROCESSING OF SEMAPHORINS FOR PREVENTION, TREATMENT, DIAGNOSIS AND PROGNOSIS OF AN INVASIVE DISEASE

(57) Abstract: The present invention relates to use of compounds directed to inhibiting expression and/or proteolytic processing semaphorins SEMA3E and/or sema3E and/or activation of a receptor by a proteolytic product of said semaphorins for the manufacture of a medicament for prevention, treatment, diagnosis and/or prognosis of an invasive disease. The invention features the compounds selected from the group comprising antisense compounds derived from the sequence of SEMA3E and/or sema3E, peptide compounds derived from the sequence of said semaphorins, anti-bodies against said semaphorins, and peptide compounds derived from the sequence of Plexin A receptor. Furthermore, the invention provides methods for prognosis and/or diagnosis of malignancy of cancer based of estimation of the levels of expression and proteolytic processing of said semaphorins in a sample of a tissue or body fluid. The invention also concerns a method for producing an attractant polypeptide by establishing a cleavage product of SEMA3E and/or sema3E.

INTERNATIONAL SEARCH REPORT

International Application No

P.T/DK 03/00486

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K38/17 C07K14/47 C07K16/18 G01N33/68 C12Q1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K G01N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 47671 A (CHRISTENSEN CLAUSE R L ; LUKANIDIN EUGENE M (DK)) 23 September 1999 (1999-09-23) page 45 - page 47, figure 4, claims, Seq ID no. 1-4	1,5-19, 28,29, 39,42, 51-53
A		20,21
Y	CLAUS R.L. CHRISTENSEN ET AL: "Transcription of a novel mouse semaphorin gene, M-semaH, correlates with the metastatic ability of mouse tumor cell lines" CANCER RESEARCH, vol. 58, 15 March 1998 (1998-03-15), pages 1238-1244, XP002263840 page 1241 and "Discussion" --- -/--	1,5-19, 28,29, 39,42, 51-53

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 December 2004

Date of mailing of the international search report

27.12.2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

PATRICK ANDERSSON /EÖ

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CRL CHRISTENSEN ET AL: "SEMA3E affects endothelial cell motility in vitro and increases lung colonisation by tumour cells in vivo" CLINICAL & EXPERIMENTAL METASTASIS, vol. 18, no. 2, 2000, XP002263841 page 109, "P161"	1,5-13, 19,39
Y	MIREIA MARTIN-SATUE ET AL: "Identification of semaphorin E gene expression in metastatic human lung adenocarcinoma cells by mRNA differential display" JOURNAL OF SURGICAL ONCOLOGY, vol. 72, 1999, pages 18-23, XP002263842 the whole document	1,5-13, 19,39
X A	---	49 47,48
Y	WO 01 51518 A (CORREA RICARDO ;SOUZO SANDRO DE (BR); SIMPSON ANDREW JOHN GEORGE () 19 July 2001 (2001-07-19) page 4 -page 5; examples 9,12,13	1,5-9, 28,29, 39,42
X	RALF H. ADAMS ET AL: "The chemorepulsive activity of secreted semaphorins is regulated by furin-dependent proteolytic processing" THE EMBO JOURNAL, vol. 16, no. 20, 1997, pages 6077-6086, XP002263843 page 6077 -page 6078 page 6082	39-41, 44,45,50
Y	table 1, figure 1 and page 6082 - page 6084 "Discussion"	1,5-19, 22-38, 42,43, 51-53
X	DANIEL E. BASSI ET AL: "Furin inhibition results in absent decreased invasiveness and tumorigenicity of human cancer cells" PNAS, vol. 98, no. 18, 28 August 2001 (2001-08-28), pages 10326-10331, XP002263844 the whole document	1,5-7, 14-21, 28,29, 34-37, 42,46,50
Y	---	22-27, 43-45
X	WO 01 14420 A (UNIV TORINO ;TAMAGNONE LUCA (IT); ARTIGIANI STEFANIA (IT); COMOGLI) 1 March 2001 (2001-03-01) examples 8,9	30-37

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MANGASSER-STEPHAN, KERSTIN ET AL: "Identification of Human Semaphorin E Gene Expression in Rheumatoid Synovial Cells by mRNA Differential Display" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 234, no. RC976607, 1997, pages 153-156, XP002286525 page 155	3,8-12, 40,41
Y	--- DELAIRE, ST PHANIE ET AL: "Biological Activity of Soluble CD100. II. Soluble CD100, Similarly to H-SemaIII, Inhibits Immune Cell Migration 1,2" IMMUNOLOGY, vol. 166, 2001, pages 4348-4354, XP002286526 Discussion page 4351	3,8-12, 40,41
X	--- JEAN, FRANCOIS ET AL: "A protein-based therapeutic for human cytomegalovirus infection" PNAS, vol. 97, no. 6, 14 March 2000 (2000-03-14), pages 2864-2869, XP002286527 page 2864	1,2,4, 8-12, 14-21, 28-33, 39,42,43
Y		22-27, 30-38, 40,44,45
A	--- NAGAHARA, HIKARU ET AL: "Transduction of full-length TAT fusion proteins into mammalian cells: TAT-p27Kip1 induces cell migration" NATURE MEDICINE, vol. 4, no. 12, December 1998 (1998-12), pages 1449-1452, XP002286528 figure 1	4
A	--- ROHM, BEATE ET AL: "The semaphorin 3A receptor may directly regulate the activity of small GTPases" FEBS, vol. 486, 2000, pages 68-72, XP002286529 figures 3,4	30-33
A	--- TAMAGNONE, LUCA ET AL: "Signalling by semaphorin receptors: cell guidance and beyond" TRENDS IN CELL BIOLOGY, vol. 10, September 2000 (2000-09), pages 377-383, XP002286530 page 380; table 1	1-53
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 34474 A (ZYMOGENETICS INC) 15 June 2000 (2000-06-15) page 4, line 16 -page 5, line 3 page 16, line 7 - line 18 page 16, line 19 - line 29; table 1 page 48, line 17 -page 50 page 72, line 18 -page 74, line 24 ---	1-3, 13-18
X	WO 01 17559 A (COMEAU MICHAEL RENE ;SPRIGGS MELANIE KAY (US); IMMUNEX CORP (US)) 15 March 2001 (2001-03-15) page 13, line 22 - line 28 page 15, line 19 -page 18 page 9, line 11 -page 10; claims ---	1-10, 14-18, 28, 30-32, 34-37, 39,42, 43,46, 50-52
X	WO 01 39793 A (HOLMES STEPHEN DUDLEY ;LEWIS CERI JOHN (GB); SMITHKLINE BEECHAM PL) 7 June 2001 (2001-06-07) page 1 -page 2; claims page 11, line 5 - line 13 page 12, line 2 -page 13, line 3; example 12 Seq ID No:2 possitions 186-189 ---	1-3,13
X	US 5 981 222 A (LAVALLIE EDWARD R ET AL) 9 November 1999 (1999-11-09) column 12, line 54 -column 15, line 41 ---	1-4
X	WO 99 45114 A (ZYMOGENETICS INC) 10 September 1999 (1999-09-10) page 2, line 23 -page 4, line 4 page 51, line 30 -page 53 page 57, line 17 -page 59, line 2 ---	1-3
X	EP 0 960 888 A (SUMITOMO PHARMA) 1 December 1999 (1999-12-01) page 7, line 39 - line 48 page 8, line 24 - line 40 ---	1-3,13
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 03/00486

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2001 (2001-03) WILLIAMSON MAGALI ET AL: "Over expression of semaphorin 3E in prostate cancer" Database accession no. PREV200100471530 XP002286548 abstract & PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL, vol. 42, March 2001 (2001-03), page 522 92nd Annual Meeting of the American Association for Cancer Research; New Orleans, LA, USA; March 24-28, 2001, March, 2001 ISSN: 0197-016X</p> <p>-----</p>	47-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 03/00486

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9947671	A	23-09-1999	WO 9947671 A2	23-09-1999
WO 0151518	A	19-07-2001	AU 3280401 A	24-07-2001
			WO 0151518 A2	19-07-2001
WO 0114420	A	01-03-2001	AU 7073800 A	19-03-2001
			WO 0114420 A2	01-03-2001
WO 0034474	A	15-06-2000	AU 764039 B2	07-08-2003
			AU 2167900 A	26-06-2000
			CA 2354325 A1	15-06-2000
			EP 1137773 A2	04-10-2001
			JP 2002531127 T	24-09-2002
			WO 0034474 A2	15-06-2000
			US 2002177193 A1	28-11-2002
			US 6432673 B1	13-08-2002
			US 2004043031 A1	04-03-2004
			US 6528050 B1	04-03-2003
			US 2002004225 A1	10-01-2002
			AU 8031700 A	30-04-2001
			WO 0128586 A1	26-04-2001
			US 2003087870 A1	08-05-2003
WO 0117559	A	15-03-2001	AU 7121900 A	10-04-2001
			WO 0117559 A1	15-03-2001
WO 0139793	A	07-06-2001	AU 2669501 A	12-06-2001
			WO 0139793 A2	07-06-2001
US 5981222	A	09-11-1999	US 5654173 A	05-08-1997
			AU 7496898 A	11-12-1998
			CA 2291477 A1	26-11-1998
			EP 1002072 A1	24-05-2000
			JP 2002503099 T	29-01-2002
			WO 9853065 A1	26-11-1998
			AU 3381797 A	06-03-1998
			CA 2263875 A1	26-02-1998
			EP 0927248 A1	07-07-1999
			JP 2000516815 T	19-12-2000
			WO 9807853 A1	26-02-1998
			US 5965693 A	12-10-1999
WO 9945114	A	10-09-1999	AU 2982799 A	20-09-1999
			WO 9945114 A2	10-09-1999
EP 0960888	A	01-12-1999	AU 4964097 A	10-06-1998
			CA 2271681 A1	28-05-1998
			EP 0960888 A1	01-12-1999
			US 6436669 B1	20-08-2002
			WO 9822504 A1	28-05-1998
			US 2002146775 A1	10-10-2002